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ORIGINAL ARTICLES

ENCEPHALOPATHIES FOLLOWING PROPHYLACTIC PERTUSSIS VACCINE

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INTRODUCTION

INFLAMMATORY reactions involving various parts of the nervous system following injections of various sera or vaccines have long been known but, so far as we are aware, no one has described the severe encephalopathies which have been observed following the prophylactic use of pertussis vaccine in infants. Madsen[1] in his report on the prophylactic inoculations of 1,832 Faroe Islanders mentioned the death of two small infants in convulsions beginning one or two hours after injections of fluid pertussis vaccine. He reported that autopsies failed to disclose any adequate cause of death. Werne and Garrow[2] reported the death in shock of a pair of identical twins 16 and 24 hours respectively after the second injection of alum-precipitated diphtheria toxoid and pertussis antigen. Careful post mortem examination showed widespread vascular injury. Convulsions, said to be ephemeral in character, have been reported by a number of observers. Doull, Shibley, and McClelland[3] reported three children with convulsions among 496 children immunized with fluid vaccine. Taylor[4] reported a reaction to the vaccine of a ten-month-old boy characterized by subnormal temperature, limpness, and convulsions coming on a few hours after the injection. Recovery was stated to be complete in a few hours. Kendrick and Eldering[5] reported the immunization of 1,815 children, 6 to 15 months of age, by 9,075 injections, with one reaction characterized by convulsions. Sako[6] and his co-workers reported two instances of convulsions following

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6,600 injections of H. pertussis alum-precipitated vaccine, and in a personal communication Sako states that in approximately 105,000 children immunized to pertussis, there have been four transient convulsions. Many large series, such as the early ones of Sauer[7] involving 3,974 children and the later one of Cravitz and Cauley[8] including 5,000 children, have been reported without reference to such accidents.

It has been accepted for years that virus vaccines, such as those of vaccinia and rabies, occasionally produce encephalopathies and myelopathies (Turnbull[9] and Bassoe[10]). The question of the occurrence of such lesions following revaccination remains obscure, since the available evidence in the literature (Comby[11] and Guerido[12]) is inconclusive. That sera and bacterial vaccines can produce similar changes has been shown by Ayer[13] for the peripheral nerves (antitetanic serum), by Kennedy[14] for peripheral nerves, cord, and brain (typhoid vaccine), and by Winkleman and Gotten[15] for various parts of the nervous system following both sera and vaccines. Curphey[16] has recently reported the death in convulsions of a three and one-half year old girl after inoculation with Influenza A and B vaccine. Autopsy showed widespread pathologic lesions, principally vascular. A reaction involving antigen and antibody has been suspected by many as a possible explanation of such disease processes, and Ferraro[17] recently has reviewed the literature on this point extensively and has added observations of his own.

That a specific toxin might be responsible for the cases reported remains another possibility, and such a product of H. pertussis was suspected by Bordet and Gengou[18] in their original description of the organism. Their observations were first amplified by Tessier[19] and his co-workers, and subsequently many workers[20-27] have described toxins produced in a variety of ways from cultures of the bacillus. All observers agreed that a toxin, or toxins, were produced by appropriate cultures, but that such products were very unstable and difficult to prepare and preserve. Since most of the above observers were interested in the antigenic properties of the toxins, autopsy studies of their effects were mentioned only incidentally. They proved fatal to mice and guinea pigs and necrotizing to the skins of rabbits. After either intravenous or intraperitoneal injection, lesions of the organs of the peritoneal cavity were the most common findings in fatal experiments.

Fonteyne and Dagnelie[28] prepared an endotoxin which produced a diffuse encephalitis and death when injected into either the cerebral substance or subarachnoid space of rabbits or guinea pigs. Various control substances produced from other organisms, or the heated pertussis endotoxin used in the same way, did not reproduce the results. Nakamura[29,30] produced encephalitic changes in rabbits with a combination of agents, among them intravenous injections of cultures of H. pertussis. He also produced both an endotoxin and an exotoxin from the same cultures which, when injected into the subarachnoid spaces of rabbits, caused a rapidly fatal encephalitis.

CLINICAL OBSERVATIONS

During the past few years, several children were admitted to the Children's Hospital in Boston in convulsions beginning a few hours after the injection of prophylactic pertussis vaccine. Their stories were so similar that during the past winter we have made a search through the records of the hospital for the past ten years, and have found 15 similar instances, which form the basis of the present report.

Twelve of the children were boys and three were girls, a sex difference also encountered in relation to other substances, such as lead, causing gross injury to the developing nervous system.[31] At inoculation time, the children varied in age between 5 and 18 months. Developmental data were obtained in detail on all but two of the children, whose mothers simply stated that they had developed normally. Reference to the case histories showed that such objective activities as sitting, walking, and talking had appeared in many of the children prior to the inoculations; and that regressions or failure of further development occurred after the encephalopathies in several instances. In so far as it was possible to judge none of the children were defective prior to their acute illness. None had had convulsions.

TABLE I

ETIOLOGIC FACTORS

Case	Age at Time of Injection	Sex	Injection Causing Reaction	Dose in Billions of Organisms	Time Interval to Onset of Symptoms	Severity of Symptoms	Residence
1	15 months	Male	3rd	?	18 hours	Severe	Fall River, Mass.
2	10 months	Male	2nd	30	1 hour	Severe	Boston, Mass.
3	12 months	Male	2nd	40	4 hours	Severe	Boston, Mass.
4	7 months	Female	3rd 4th	40 12	4 hours 12 hours	Severe Severe	Hartford, Conn.
5	18 months	Male	1st	40	20 minutes	Moderate	Boston, Mass.
6	8 months	Male	1st 2nd	20 30	8 hours 72 hours	Mild Severe	Arlington, Mass.
7	11 months	Male	3rd	40	8 hours	Severe	Medford, Mass.
8	10 months	Male	1st	20	6 hours	Severe	Boston, Mass.
9	6 months	Male	3rd	45	11 hours	Severe	Newton, Mass.
10	9 months	Male	1st	20	20 minutes	Severe	Fall River, Mass.
11	5 months	Female	1st	?	6 hours	Severe	Fisher's Island, Conn.
12	7 months	Male	3rd	40	24 hours	Severe	Boston, Mass.
13	6 months	Male	2nd	40	24 hours	Severe	Salem, Mass.
14	6 months	Male	1st 2nd	10 10	12 hours 12 hours	Severe Severe	Quincy, Mass.
15	7 months	Female	3rd	10	10 hours	Severe	Putnam, Conn.

Family histories were of interest in respect to three patients. In Case 2, two out of three siblings had epilepsy, apparently idiopathic, and an uncle was hydrocephalic. One of two siblings of Case 9 was hydrocephalic and, finally, a younger sibling of Case 12 had "febrile convulsions" five years after the onset of the patient's illness.

The injections were given between 1939 and 1947. There was no concentration in any one year. No cases originated in 1940 and 1942, and the number of cases in each of the other years varied from one to four. Geographically, the patients came, as would be expected, from Greater Boston in nine instances, two were from Fall River, Mass., and one each from Hartford, Conn., Fisher's Island, Conn., Putnam, Conn., and Salem, Mass.

The only common precipitating agent was some form of pertussis vaccine. In 12 instances fluid pertussis vaccine was used, in two cases combined diphtheria toxoid (in one instance fluid and in the other alum-precipitated) and fluid pertussis vaccine was used, in one case the triple antigen of diphtheria and tetanus alum-precipitated toxoid and fluid pertussis vaccine was used, and in one case the triple antigen, all of whose components had been treated with alum, was used. The usual dosage schedule of three doses, respectively, 20 billion, 40 billion, and 40 billion bacteria or less was used in all instances save one, in which an initial dose of 40 billion bacteria was followed in a matter of minutes by irritability, coma, fever, and convulsions. In two instances the size of the dose was not recorded. Six children reacted explosively to the first dose, three to the second dose, and six to the third dose. In addition, three children, who had had convulsive reactions to an earlier dose, reacted again with convulsions following a succeeding dose.

The products of eight different manufacturers were identified by the doctors who gave the inoculations as having been used. Although one manufacturer was represented five times and another three times, these two between them supply a large proportion of the biologicals used in and about Boston.

The explosive reactions began as soon as 20 minutes and as long as 72 hours after the inoculations. The outstanding symptom among the group was convulsions, which varied from a few minutes to several days in duration. Changes in consciousness, varying from drowsiness or irritability to deep coma, occurred in all. It is noteworthy that milder reactions had occurred following an earlier dose of vaccine in two instances; one patient was irritable and had a blotchy rash and a second was feverish and lethargic for two days.

Six of the patients were admitted to the hospital at the time of the acute episodes. All showed various neurologic signs associated with cerebral disease, five were described as comatose, four had hemiplegia, and two had generalized hyperreflexia with bilateral clonus and Babinski signs. In none were the ocular fundi abnormal.

Spinal fluid examinations on these six children were normal in one; i.e. no cells and total protein 29 mg./100 cc. fluid. In the remainder the total protein varied from 35 mg./100 cc. to 86 mg./100 cc., and the cell counts from 0 to 35 mononuclear cells per cmm. Two spinal fluids were examined in other hospitals at the time of the acute attacks: one was reported as normal and the other showed a negative Pandy test and 63 monocytes per cmm. White blood cell counts on the acutely ill patients varied from 10,000 to 20,000 per cmm., and the predominant cells were polynuclear neutrophiles in proportions from 58% to 86%.

In the whole series, the acute illness varied in length from 36 hours to 10 days. After this, one child had three convulsions scattered over a five month period, but in the two year follow-up period had remained well and development seemed satisfactory to his mother. The remaining 14 children suffered from a variety of continuing difficulties, because of which nine were brought to the hospital for the first time. It is obvious that this method of selections of patients probably weighted the series with individuals who did badly.

Intellectually, 4 infants between 11 and 26 months of age appeared intact 4 to 14 months after their acute illness. One child, seen only once, one month after discharge from the hospital, had not yet regained his speech, which had been present before the inoculations. A sixth infant, who had recurrent convulsions for two months after his encephalopathy, had a complete remission of convulsions for four months following pneumoencephalography. Although he still showed a mild right hemiplegia, his mother felt that his development, while slower than that of his older siblings, was accelerating.

TABLE II

Final Status

Case	Follow-Up Age in Months	Time in Months Since Vaccine	Examination		EEG	PEG
			Neuro.	Mental		
1	32	17	C.P. *	+	Normal	Not done
2	19	9	C.P. *	±	Normal	Enlarged ventricles
3	31	19	*	+	Normal	Not done
4	48	38	*	−	3 sec. Wave & spike	Enlarged ventricles
5	19	1	C.P.	+	Not done	Not done
6	20	12	C.P. Blind	−	3–5 sec. Slowed	Enlarged ventricles
7	14	3	C.P. * *	+	Slow wave. Focus left	R. vent. >l. ? normal
8	30	20	Died of pneumonia *	 −		
9	12	6	Died of pneumonia		Not done	Enlarged ventricles. r. >l.
10	76	66	*	−	Slow & fast	Enlarged ventricles
11	32	27	C.P. Blind	−	2 sec. Wave & spike	Enlarged ventricles
12	8 yrs.	90	*	−	Spike focus. Left temporal	Enlarged r. lateral ventricle
13	34	28	Normal	+	Normal	Not done
14	17	11	*	−	3–5 sec. Slowed	Enlarged ventricle
15	11	4	*	+	2½–4 sec. Slowed	Normal

C.P. Cerebral palsy.
* Recurrent convulsions.
+ Normal mentality.
− Retarded mentality.

A seventh patient had a four month period following his acute episode, during which he appeared to be developing normally, only to go into status epilepticus when 14 months of age, at the onset of an upper respiratory infection. From this time on he pursued a steadily deteriorating course, ending in death in an institution. The remaining eight patients showed more or less severe retardation. In several instances, such as Cases 3, 7, and 8, development had progressed far enough prior to the inoculation to allow a clear statement of intellectual regression after the acute episode. Four children, who had inoculations four years or more ago, were given psychologic examinations by Dr. Edith Meyer during the past winter. All showed defects of attention, irregularities of mental development most marked in relation to abstract behavior, and difficulty in organizing material; in short the sort of psychologic variations found by a number of writers[32-34] to result from diffuse postnatal brain injury. Three children were grossly defective, of whom one (in addition to the child mentioned above) died, also in an institution.

Recurrent convulsions, either grand mal, petit mal, or localized in type, continued over variable lengths of time in 13 children. In three of these, remissions varying in length from three months to two years have occurred, but in the remaining ten the convulsions have continued either to the death of the patient or to the present time.

Seven of the living children, at the time of the last contact, showed other evidences of cerebral damage: five had hemiplegias and two were virtually decerebrate. Among these, Cases 1, 3, 5, and 7 were walking without evidence of cerebral palsy prior to their inoculations.

In summary, therefore, one child had recovered completely, three had had too short a period of observation to allow for final conclusions, two pursued a long down-hill course ending in death, and the remaining nine suffered from damage to their nervous system, which in most instances promised to interfere with competitive living.

Of eight pneumoencephalograms done during the follow-up period, six showed dilatation of the ventricular system and two were at the upper limit of normal. Of ten electroencephalograms, six were normal and the remaining four were abnormal.

TABLE III

Encephalopathy During Pertussis—26 Cases
7 Months and Under—13 Cases

Outcome	
Satisfactory to family	6
Mental retardation	6
Chronic convulsions	3
Cerebral palsy	1
Dead	7
Unknown	3

To control the possibility that coincidence played an important part in the production of these encephalopathies following pertussis vaccine, the hospital records were consulted as to the incidence of vaccinial encephalitis. Since Massachusetts has a law requiring all children be vaccinated prior to school admission, it seemed certain that a greater proportion of the population were exposed to this vaccine than to pertussis vaccine. That vaccination is a cause of encephalomyelitis is well established (Bijl[35] and Finley[36]). During the same ten years there were admitted to the Children's Hospital eight cases of this latter condition. Either the encephalopathy following pertussis vaccine must be more common, under present conditions of usage, or more severe or more devastating than that following vaccination against smallpox, since it seems doubtful if more than one-quarter of the children in Massachusetts receive pertussis vaccine. It should be noted that pertussis vaccine is used largely in infancy and smallpox vaccine, by and large, is used in this state as children approach school age. The literature would lead one to suspect that smallpox vaccination was accompanied by a greater risk at five years than in infancy, while the reverse may be true of pertussis vaccine. Though some of the children with encephalopathy following pertussis vaccine came from states other than Massachusetts, vaccination customs are virtually the same in them.

During this same ten year period, there were also admitted to the Children's Hospital 26 children suffering from the acute or chronic effects of encephalopathy accompanying pertussis itself. Of these, 13, or one-half, were seven-months-old or younger and would not have had time since birth to be immunized according to the usual practice at present in vogue. Of these small infants, one had had a single dose of hyperimmune serum during the incubation period; otherwise no prophylactic treatment had been attempted. Among the 13 older children, one had had a course of pertussis vaccine ending approximately six weeks prior to the onset of her pertussis, and another had received two doses of pertussis vaccine as treatment for her disease. Her encephalopathy began explosively 18 hours after the vaccine, and might just as well be charged to the vaccine as to the pertussis.

Of the entire group of 26 children with encephalopathy following pertussis, six were satisfactory to their families six months to ten years after their acute illness, seven died of their acute illness, three could not be found, and the remaining ten were sufficiently damaged to make competitive living unlikely. Good and bad outcomes seemed for this small group to be impartially distributed between the younger and older children.

SUMMARY

Inspection of the records of the Children's Hospital for the past ten years has disclosed 15 instances in which children developed acute cerebral symptoms within a period of hours after the administration of pertussis vaccine. The children varied between 5 and 18 months in age and, in so far as it is possible to judge children of this age range, were developing normally according to histories supplied by their parents. None had had convulsions previously. Many different lots of vaccine, made by eight different manufacturers over a period of eight years, were implicated. The inoculations were given throughout the usual geographic range of children coming to this hospital. All but one, at the time of follow-up or death, showed evidence of impairment of the nervous system, which might still have been in the healing stage in three or four.

During the same period about half as many children were seen in the hospital suffering from the encephalopathy secondary to smallpox vaccination, and about twice as many from the encephalopathy complicating pertussis itself.

A variety of etiologic considerations were suggested by consideration of the reported cases and references to the literature. That constitutional factors may have been involved was suggested by both the preponderance of males as opposed to females, and by the high incidence of abnormalities of the nervous system in the family histories. The clinical course and cytologic abnormalities of spinal fluids found in acute cases indicated an encephalopathy. The literature suggested that this process might have resulted from either the activity of a specific toxin or from an antigen-antibody response. Against the former of these hypotheses was the unstable nature of the heretofore recognized toxins which could hardly survive in properly aged vaccines. The rapid onset of symptoms, occasionally within minutes of the first injection, seemed strong evidence against the second. The present study has left these etiologic considerations unanswered, but it has called attention to a risk of the prophylactic use of pertussis vaccine not hitherto recognized.

In view of the impressive evidence of the effectiveness of prophylactic pertussis vaccine now accumulating, it seems likely that babies are safer vaccinated than not. Further studies should be made to prove this point definitely, for the encephalopathy following pertussis vaccine seems more devastating than the vast majority of the nervous lesions following the use of smallpox vaccine.

CONCLUSION

In common with many other biologic materials used parenterally, an important risk of encephalopathy attends the use of prophylactic pertussis vaccine. The mechanism whereby the encephalopathy is produced is not elucidated by the present study. The universal use of such vaccine is warranted only if it can be shown to be effective in preventing encephalopathy or death from pertussis itself in large groups of children. If avoidance of the inconvenience of the average attack of pertussis is all that is expected, the risk seems considerable. Efforts to diminish the hazard by modification of the vaccine or new methods of administration seem indicated.

CASE HISTORIES

#1, D.H. (Seen through the kindness of Dr. Bronson Crothers). Male—21 months. Entered because of left hemiparesis. Family History: F., M., and two siblings living and well. Past History: Normal, walking, talking. Present Illness: At about 14 months given first two inoculations of combined diphtheria toxoid (alum-precipitated) and pertussis vaccine. At 15 months, in April 1945, in Fall River, Mass., given third inoculation of diphtheria toxoid (alum-precipitated) and pertussis vaccine (amount and manufacturer unknown). Eighteen hours later developed a fever of 40.5° C. and had a severe left-sided convulsion, which was controlled finally with sodium phenobarbital. Following the convulsion, was unresponsive and had a spastic left hemiplegia. Admitted to another hospital, where he continued to have left-sided convulsions. These gradually diminished, and the left hemiparesis improved. Laboratory findings: WBC 20,000/cmm. with 58% polynuclear leucocytes and normal spinal fluid. Discharged very much improved, but with a persistent left hemiparesis. Course: Seen at the Children's Hospital at 21 months. Had had four convulsions in the interval, but otherwise had shown gradual improvement. Examination at that time showed an intellectually able child with a left hemipareis. EEG was normal, showing 6-8 per second waves, with scattered 4's and 5's and no focus. PEG was not done. At 24 months parents wrote that he continued to improve and had no more seizures.

#2, J.R. Male—18 months. Entered because of recurrent convulsions. Family History: F. and M. living and well. Three siblings, of whom two have epilepsy. Past History: Normal, walking. Present Illness: At ten months, in July 1946, in Boston, was given first inoculation of pertussis vaccine (amount and manufacturer unknown) without reaction. Several weeks later received second immunizing dose of 1.5 cc. pertussis vaccine (30 billion organisms—manufacturer "A"). One hour later developed fever and had a severe generalized convulsion. This was followed by stupor, which gradually cleared in three days. Since that time had had recurrent right sided convulsions. Course: At 18 months was admitted to the Children's Hospital. At that time was found to have a moderate right hemiparesis. Psychologic examination revealed a relatively efficient and competent individual. Laboratory findings: WBC 9,200/cmm. negative blood Hinton, and normal spinal fluid with total protein of 13.8 mg./100 cc. fluid. EEG showed 3-5 per second waves with a little 6 per second activity, and was considered normal. PEG (Fig. 1.) revealed considerable symmetrical dilatation of entire ventricular system, basal cisterns, and filled subarachnoid passages compatible with diffuse deficiency of cerebral and cerebellar tissues. Continued to have right-sided convulsions but was improved with phenobarbital. Developmental rate did not seem impaird by his illness.

#3, B.L. Male—25 months. Entered because of convulsive seizures. Family History: F., M., and one sibling living and well. Past History: Normal, walking. Present Illness: At 11 months received 1 cc. pertussis vaccine (manufacturer "B") without reaction. At 12 months, in December 1945, in Boston, received second inoculation of 2 cc. pertussis vaccine (40 billion organisms—manufacturer "B"). Four hours later had a severe generalized convulsion, followed by a right-sided hemiparesis. Entered another hospital where a gradual improvement was noticed within ten days. Following this seemed well until 19 months when he developed recurrent petit mal seizures, which became more frequent. Course: At 26 months admitted to Children's Hospital. Examination was essentially normal except that he did not talk and dragged right leg in walking. Mental status was considered probably normal. Laboratory findings: WBC 7,300/cmm. with 55% polynuclear leucocytes, negative blood Hinton, and negative X-rays of the skull. EEG was considered normal, and showed 4-7 per second waves without focus or seizure discharges. PEG was not done. Attacks had

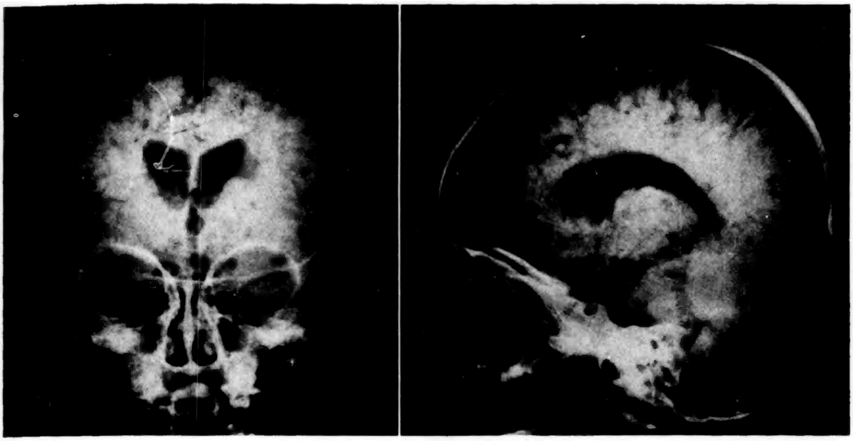

FIG. 1. Pneumoencephalogram in Case 2 seven months after inoculation, showing slight dilatation of lateral and third ventricles.

not been controlled by various drugs. At 31 months intellectual status had not advanced beyond that found at 26 months, and was definitely retarded and irregular. Had not developed speech, and was having many attacks weekly, which were uncontrolled by a variety of drugs. Physical examination showed a very obvious right hemiplegia with contractures of the heel cord. An electroencephalogram (Fig. 2.) showed a few scattered spikes and a good many slow waves, at the rate of 3-4 per second, most marked in right occipital lead.

#4, J.P. Female—10 months. Entered because of recurrent convulsions. Family History: F. and M. living and well. No siblings. Past History: Normal, sat alone at seven months. Present Illness: At about seven months was started on a course of immunization for pertussis, and had first and second inoculations without incident (manufacturer "C"—amount unknown). At seven and one-half months, in September 1943, in Hartford, Conn., was given third pertussis inoculation of 2 cc. pertussis vaccine (40 billion organisms—manufacturer "C"). Six hours later developed a high

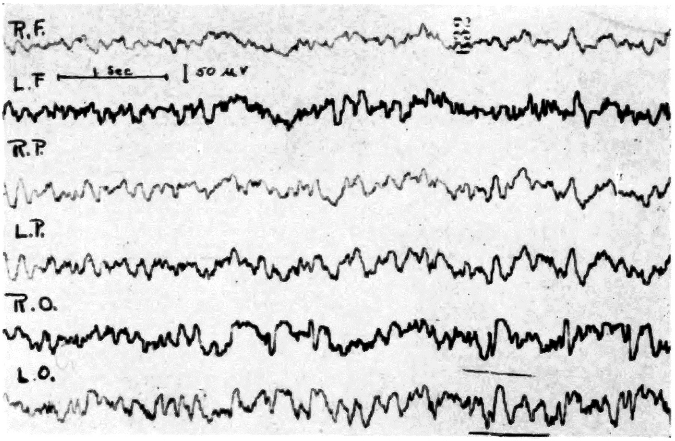

FIG. 2. Electroencephalogram in Case 3 showing spike in occipital leads, 19 months after inoculation.

fever and had a severe generalized convulsion. In the next few days had three or four more generalized convulsions, which were treated symptomatically, and recovered promptly without sequelae. Three weeks after the third pertussis inoculation, a fourth was given, of 0.3 cc. pertussis vaccine, doubly concentrated, precipitated (about 12 billion organisms—manufacturer "D"). Twenty-four hours later again had a severe generalized convulsion. Again recovered promptly, but since that time development seemed to be retarded. Course: At 10 months admitted to the Children's Hospital. At that time appeared well but somewhat retarded for age, in that she did not sit up or pull up. Laboratory studies: Normal urine, WBC 6,150/cmm. with 64% polynuclear leucocytes, and a clear spinal fluid with total protein of 9.5 mg./100 cc. fluid. Subdural taps were negative. EEG showed abnormally slow activity with several three per second waves and spike discharges and amplitude asymmetry, with higher voltage on left. PEG (Fig. 3.) revealed moderate dilatation of lateral ventricles, third ventricle, and aqueduct. Basal cisterns and subarachnoid pathways were also dilated. The appearance was considered campatible with a moderate and diffuse deficiency of

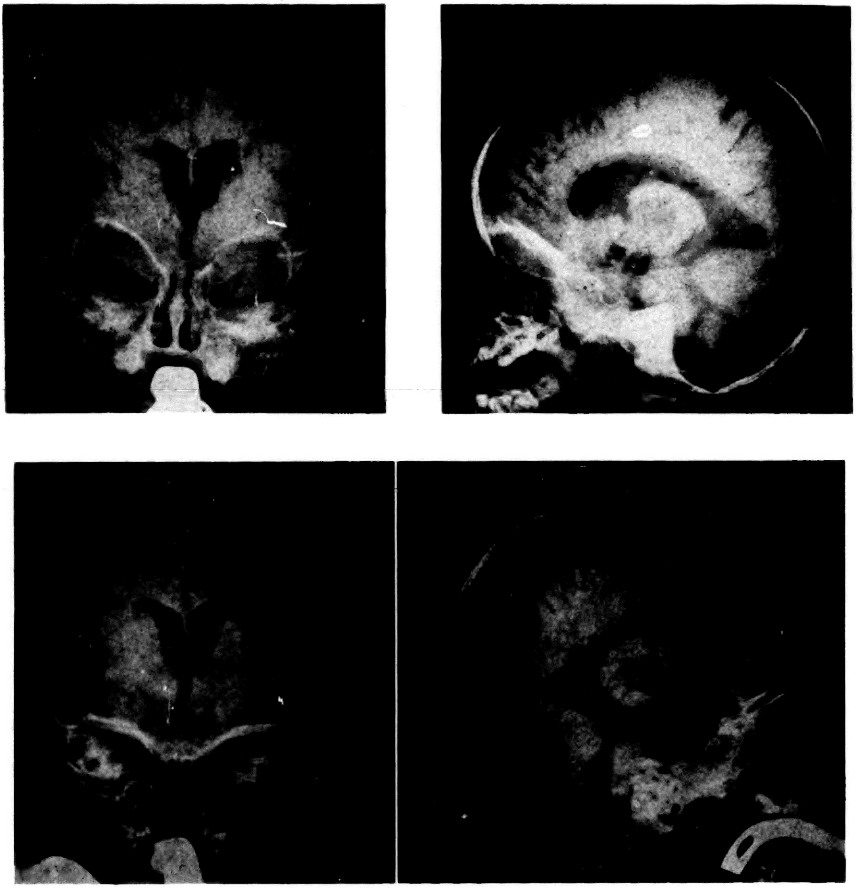

FIG. 3. Pneumoencephalograms in Case 4 two months and twelve months after last inoculation of pertussis vaccine, the second series showing some restitution of brain mass, though the lateral and third ventricles are still mildly dilated.

cerebral tissues. Following discharge development progressed satisfactorily, but she had numerous petit mal and occasional grand mal seizures. Was readmitted to Children's Hospital at 21 months for reevaluation. At that time she seemed to be a competent child who had developed normally, but who had numerous petit mal seizures. Repeat EEG (Fig. 4.) showed 3 to 7 per second waves in all leads, with occasional bursts of petit mal wave and spike. PEG (Fig. 3.) revealed slight persistent symmetrical dilatation of the entire ventricular system and basal cisterns. She was discharged on trimethadione (tridione) and has continued to improve, with gradual lessening of the petit mal, although her mother considers her development still somewhat retarded. Letter from mother at four years states condition is about the same.

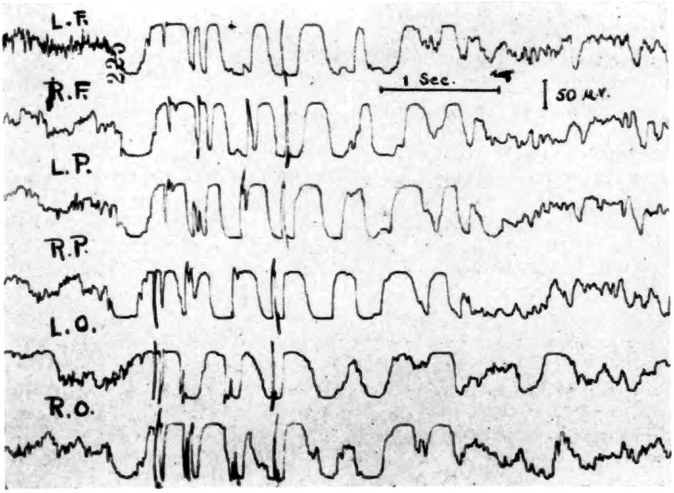

FIG. 4. Electroencephalogram in Case 4 showing wave and spike complexes three years after last inoculation of pertussis vaccine.

#5, J.M. Male—18 months. Entered because of coma of 24 hours' duration. Family History: F. and M. living and well. One sibling in third week of whooping cough. Past History: Normal, walking. Present Illness: Because of family exposure to pertussis was given at 18 months, in May 1945, in Boston, first inoculation of 2 cc. pertussis vaccine (40 billion organisms—manufacturer "E"). About 10 to 20 minutes later became drowsy, then unresponsive, rigid, and febrile. Because of continuing intermittent generalized convulsions, was admitted to Children's Hospital 24 hours later. Course: Examination showed a well developed child in semicomatose state, responding only to painful stimuli. Deep reflexes were exaggerated, and bilateral Babinskis, Oppenheims, and ankle clonus were obtained. Laboratory findings: Normal urine, WBC 10,000/cmm. with 64% polynuclear leucocytes, negative blood Hinton, and negative 1-1000 tuberculin skin test. Throat cultures for pertussis were negative and spinal fluid was normal except for a total protein of 49.5 mg./100 cc. fluid. Was treated symptomatically and improved rapidly, although he never spoke while in the hospital. When seen at 19 months had a slight right hemiparesis, brought out on walking. Was learning a few words and seemed fairly competent. PEG and EEG not done.

#6, R.M. Male—8 months. Entered because of convulsions of three weeks' duration. Family History: F., M., and one sibling living and well. Past History: Normal, held head up at five months and was rolling over at seven months. Present Illness: At seven months was given first inoculation of 1 cc. pertussis vaccine (20 billion organisms—manufacturer "E"). Following this developed irritability and drowsiness, which cleared in about three days. Three weeks later, in December 1944, in Arlington, Mass., was given second inoculation of pertussis vaccine, 1.5 cc. (30 billion organisms—manufacturer "E"). Rapidly became irritable, restless, febrile, and held right arm stiffly. About 72 hours after the inoculation had two severe generalized convulsions and was admitted to another hospital. On admission was febrile and was having generalized convulsive seizures. Lumbar puncture revealed clear spinal fluid with a total protein of 26 mg./100 cc. fluid. WBC was 10,000. Had repeated convulsions and improved very slowly. X-rays of the long bones, subdural taps, and repeated lumbar taps were done, but none was contributory. Nineteen days after onset was admitted to Children's Hospital. Course: On admission, at eight months was semi-comatose, febrile, and rigid, more marked on the right. Initial laboratory studies: Leucocytosis of 20,000, normal spinal fluid, and negative blood Hinton and tuberculin skin test. Had intermittent convulsive seizures controlled with phenobarbital. EEG showed 3 to 5 per second waves without seizure discharges, which was considered normal for age. PEG (Fig. 5.) revealed marked symmetrical dilatation of each lateral ventricle. Third and fourth ventricles were adequately visualized, but the basal cistern appeared dilated and some subdural air was present. Showed little improvement during hospitalization. When seen by his family physician 8 months after discharge, at 16 months, he was blind, deaf, spastic, and helpless.

#7, P.Q. Male—11 months. Entered because of convulsions. Family History: F., M., and two siblings living and well. Past History: Normal, sat alone at 7 months and walked at 11 months. Present Illness: At nine months received first inoculation of combined diphtheria toxoid and pertussis vaccine. The second dose was given at ten months of age, following which he had fever for several days. At 11 months, in December 1946, in Medford, Mass., received third dose of fluid diphtheria toxoid and fluid pertussis vaccine (40 billion organisms—manufacturer "E"). Eight hours later had a severe right-sided convulsion controlled only with sedation. Because of the convulsion, was admitted to Children's Hospital. Course: On admission was febrile and was having a right-sided convulsion. Examination was otherwise negative. WBC was 13,000 with 71% polynuclear leucocytes. Spinal fluid had normal sugar, 3 monoclear cells, and a total protein of 51 mg./100 cc. fluid. Cultures were negative. Blood Hinton and tuberculin skin test, 1-1000 and 1-100, were negative. Skull X-ray films were negative. Convulsions were controlled with sedation, and he soon became responsive, but a slight hemiplegia persisted. EEG showed 1 to 3 per second waves with some 4 to 6 per second waves, and the slowing was more marked in the whole left hemisphere in the waking record. The sleep record showed more slowing on left with amplitude asymmetry. This was interpreted as a grossly slowed EEG with slow wave focus in left hemisphere and amplitude asymmetry, with higher voltage on left. At 13 months seemed improved but continued to have right side convulsive seizures and a persistent right hemiplegia. PEG (Fig. 6.) demonstrated that the ventricular system was top normal in size. Left posterior horn appeared considerably larger than right. Basal cisterns were normal in size, except that cisterna pontis appeared enlarged. Subarachnoid, subdural, subtentorial air was visualized. At 16 months he still had mild hemiplegia, was pulling himself to his feet on furniture and drooled constantly. Had had no convulsions in the past four months. His mother felt that he was not learning as rapidly as her two older children at the same age, though obviously improving.

#8, H.G. Male—10 months. Entered because of convulsions. Family History: F., M., and one sibling living and well. Past History: Normal except for spasmus nutans, for which he was seen in the Out-Patient Department. At that time he seemed competent. Present Illness: At ten months, on September 16, 1941, in Boston, was given first inoculation of pertussis vaccine (20 billion organisms—manufacturer "F"). Soon afterward developed fever and irritability. Six hours later had a generalized convulsion and was admitted to Children's Hospital. Course: On admission was febrile and was having a generalized convulsion. WBC was 10,000 with 86% polynuclear leucocytes. Urine, blood Hinton, skull X-ray films, and tuberculin skin test, 1-1000, were negative. Spinal fluid was negative except for the total protein of 70 mg./100 cc. fluid. In the hospital he soon became afebrile and convalesced rapidly, and at 14 months was walking and beginning to say a few words. Remained well until 14 months when he again had a severe generalized convulsion. Was readmitted to Children's Hospital. Examination revealed a febrile child having generalized convulsions. There was a mild upper respiratory infection. Laboratory findings at that time: Leucocytosis of 26,000 with 55% polynuclear leucocytes, and clear spinal fluid with a total protein of 15 mg./100 cc. fluid. Blood

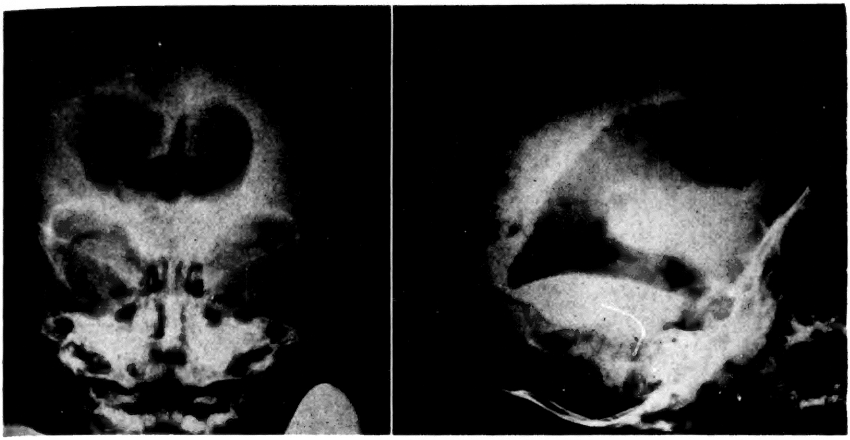

FIG. 5. Pneumoencephalogram in Case 6 one month after last inoculation of pertussis vaccine, showing enormous dilatation of the ventricular system.

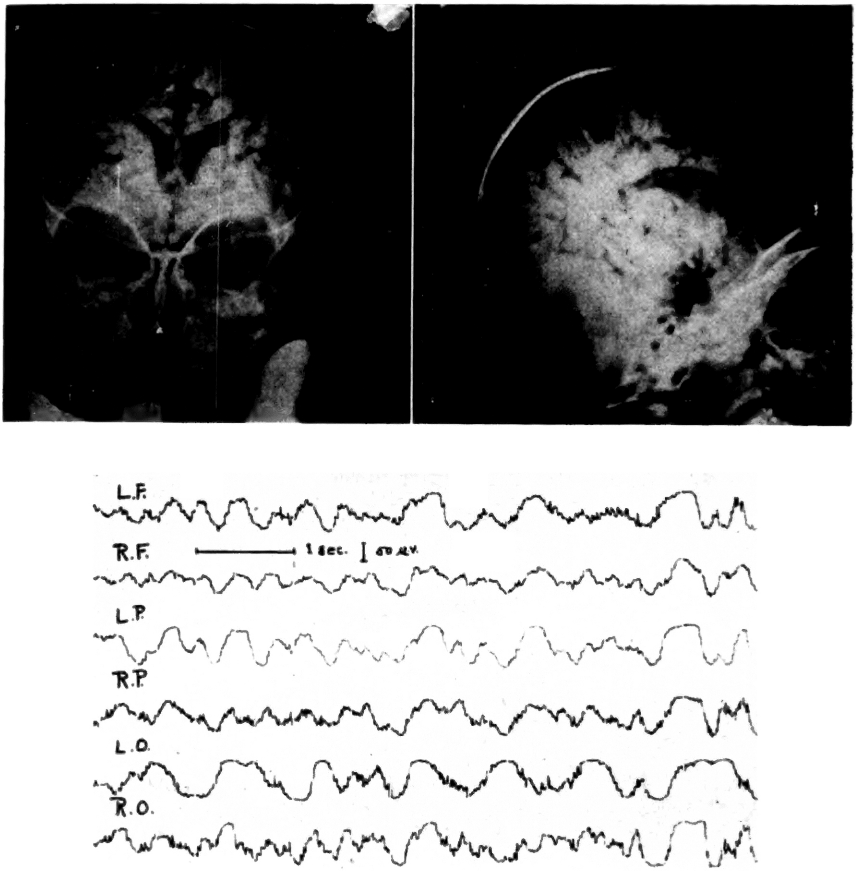

FIG. 6. Pneumoencephalogram and electroencephalogram in Case 7 two months after pertussis vaccine and diphtheria toxoid. Slight asymmetry of lateral ventricles, left being larger, and left slow wave focus involving entire hemisphere respectively.

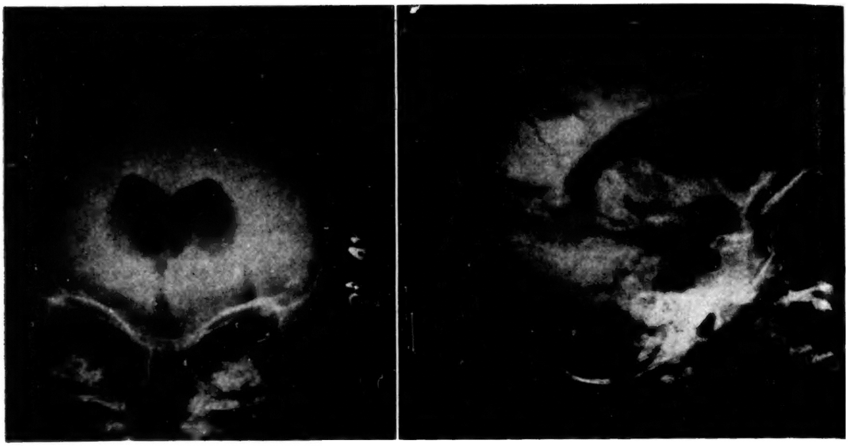

FIG. 7. Pneumoencephalogram in Case 9 one month after last dose of pertussis vaccine, showing moderate dilatation of lateral and third ventricles.

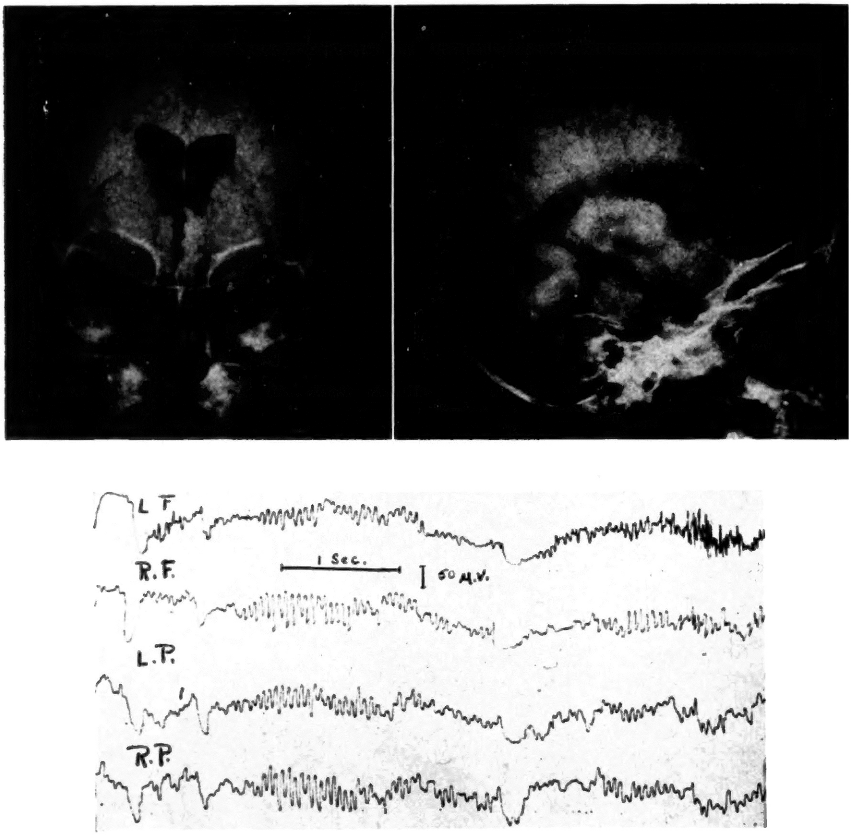

FIG. 8. Pneumoencephalogram and electroencephalogram in Case 10 three and one-half years after last dose of pertussis vaccine, showing moderate dilatation of the ventricular system and bursts of rather high voltage fast activity respectively.

culture showed pneumococcus, type XIV, in one flask. Convulsions persisted and were controlled with difficulty. The infection was controlled with sulfadiazine. Bilateral otitis media developed. Myringotomies were performed with the release of pus. However, the patient deteriorated rapidly, both psychologically and neurologically. In search of a cause for the deterioration, bilateral antrotomies were done, which were negative. PEG showed considerable air in subdural spaces and dilatation of both lateral ventricles, most marked on the left. Many subarachnoid pathways were also dilated. He did not improve and, at 16 months was transferred to a state institution where he pursued a down-hill course ending in death at two and one-half years. Autopsy done then showed diffuse atrophy and gliosis of brain with terminal pneumonia.

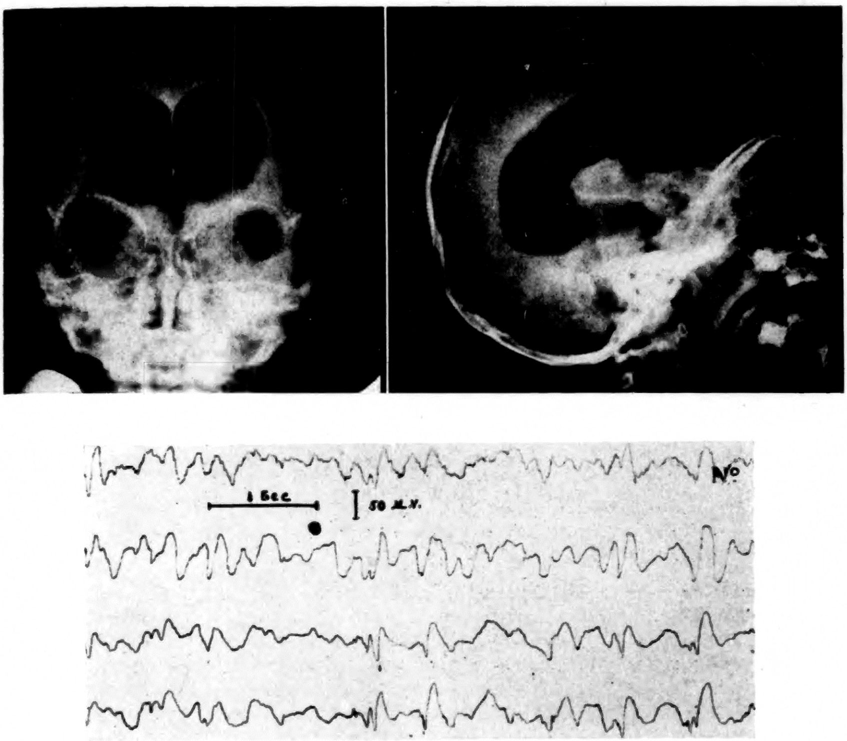

FIG. 9. Pneumoencephalogram and electroencephalogram in Case 11 two years after last inoculation of pertussis vaccine. Patient had had many acute infections and acute glomerulonephritis accompanied by convulsions in the interval. Enormous dilatation of lateral and third ventricles and many spikes in all leads.

#9, R.M. Male—6 months. Entered because of convulsions. Family History: F., M., and one sibling living and well. Another sibling had hydrocephalus and was institutionalized. Past History: Normal, held his head up at two months and sat with support at six months. Present Illness: At four and one-half months received first inoculation of 1 cc. pertussis vaccine (15 billion organisms—manufacturer "F"). The second dose of 2 cc. pertussis vaccine (30 billion organisms—manufacturer "F") was given at five months, followed by generalized maculopapular rash. The rash cleared in three days without sequelae. Third dose was given on September 22, 1941, in Newton, Mass., at six months, of 3 cc. pertussis vaccine (45 billion organisms—manufacturer "F") and was followed by fever, irritability, and 11 hours later by a generalized convulsion. The convulsion soon recurred and on this account was admitted to Children's Hospital. Course: On admission was stuporous and the odor of paraldehyde was apparent on his breath. Reflexes were hyperactive, and bilateral Babinskis and ankle clonus were obtained. Laboratory findings: Negative urine, blood Hinton, and tuberculin skin test 1-1000. Spinal fluid was clear with a total protein of 29 mg./100 cc. fluid. WBC was 17,000 with 67% polynuclear leucocytes. He improved rapidly and was discharged only to be readmitted four days later because of recurrent convulsions. Examination and laboratory findings were essentially the same as on previous admission. Convulsions persisted throughout the hospital stay. PEG (Fig. 7.) showed moderate dilatation of ventricular system without any filling defect. The left subarachnoid pathways did not fill but those on right were dilated. There was obvious severe cerebral degeneration, and the patient was discharged to a state institution for care, where he died about six months later of pneumonia. No autopsy was obtained.

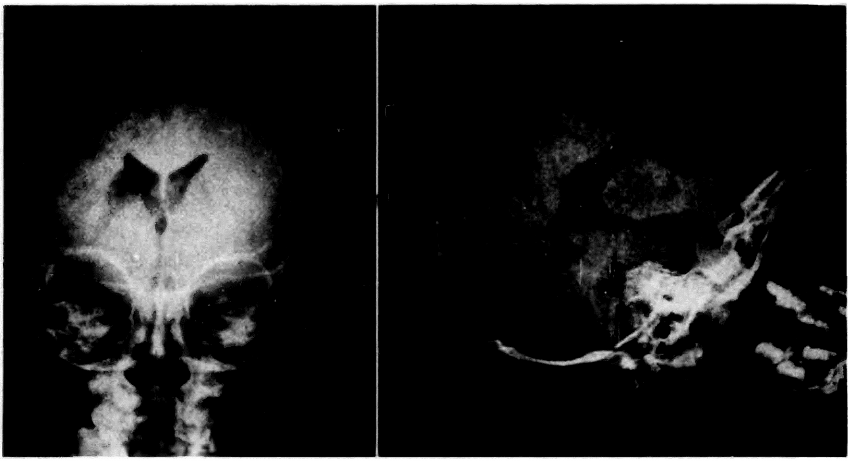

FIG. 10-a. Pneumoencephalogram in Case 12 showing localized dilatation of posterior horn of left lateral ventricle, two years after last dose of pertussis vaccine.

#10, S.W. Male—4 2/12 years. Entered because of convulsions. Family History: F., M., and one sibling living and well. Past History: Normal, held his head up at four months and was sitting at eight months. Present Illness: At nine months, in December 1941, in Fall River, Mass., was given first inoculation of 1 cc. pertussis vaccine (10 billion organisms—manufacturer "F"). One hour later developed fever of 40.0° C. and had several generalized convulsions. Following this he had had repeated generalized convulsions, frequently, but not always associated with fever. Because of recurrent convulsions and rather slow development, was admitted to Children's Hospital. Course: Examination at that time revealed immature and irregular adaptive behavior, short interest spans, and general comprehension between two and one-half and three year levels. Laboratory findings; normal urine, WBC 7,500, and clear spinal fluid without increased protein. EEG (Fig. 8.) showed 5-8 per second waves, with frequent bursts of high voltage waves. There were 12-22 per second waves in frontoparietal leads and runs of 3½-4 per second waves in all leads. This was interpreted as a slowing of waves with bursts of abnormally fast activity in frontoparietal leads. PEG (Fig. 8.) showed slight enlargement of both lateral ventricles without filling defect. Third and fourth ventricles were very slightly dilated and basal cisterns and subarachnoid pathways were normal. The patient was discharged unimproved. At six and four-twelfths years of age psychologic examination was still much the same; there had been some increase in language development, but difficulties of attention and deficiencies in relation to special orientation were as marked as ever. He had been unable to learn at all in the first grade and had been excluded from school. Convulsions had occurred at intervals of months.

#11, D.E. Female—2 8/12 years. Entered because of recurrent convulsions. Family History: F., M., and three siblings living and well. Past History: Normal. Present Illness: At five months, in January 1944, at Fisher's Island, Conn., was given one inoculation of pertussis vaccine, (amount and manufacturer unknown). Six hours later developed a generalized convulsion. Since that time had had recurrent convulsions with progressive deterioration of the nervous system. Was hospitalized several times with no improvement. On one admission, at about 2 2/12 years, was said to have had acute glomerulonephritis, but this apparently cleared promptly. Because of severe deterioration and recurrent convulsions was admitted to Children's Hospital. Course: On admission appeared grossly damaged, generally spastic, and utterly helpless. The urine and blood Hinton were negative. WBC 18,100, and there was clear spinal fluid with total protein of 25.5 mg./100 cc. fluid. EEG (Fig. 9) showed 3-5 per second waves with scattered 2 per second, and runs of positive spike discharges in both precentral leads. Slow waves and spikes were also seen in occipitals and both precentral leads. This was interpreted as a seizure record. PEG (Fig. 9.) showed marked dilatation of all ventricles. Basal cisterns were of top normal size, and there were markedly dilated subarachnoid pathways in frontal region. Appearance was that of severe and diffuse deficiency of cerebral tissue. A report from the parents at 3 4/12 years states that she continued to have convulsive seizures and was unable to stand or talk.

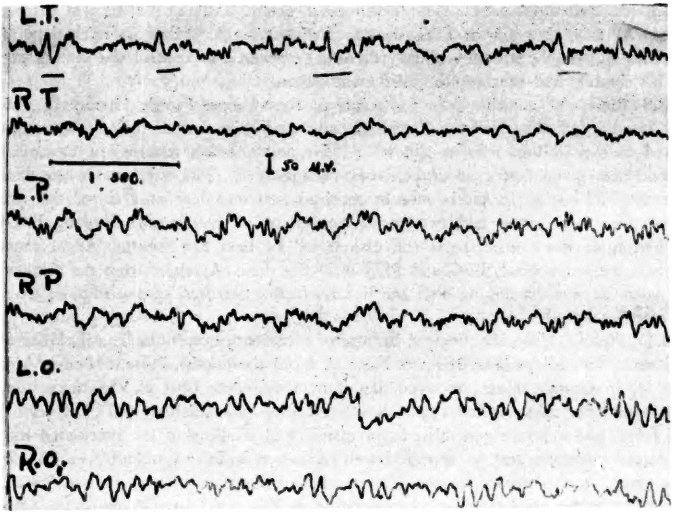

FIG. 10-b. Electroencephalogram showing left temporal spike focus, eight years after vaccine.

#12, S.C. Male—7½ months. Entered because of convulsions. Family History: F., and M., living and well. Two younger siblings, one of whom developed "febrile convulsions" five years after the patient's illness began. Past History: Normal, sat alone at six months and was pulling to his feet at seven months. Present Illness: At about seven months was given first inoculation of pertussis vaccine (20 billion organisms), and one week later second inoculation (40 billion organisms) without reaction. At seven and one-half months, on April 21, 1939, in Boston, was given third inoculation of pertussis vaccine (40 billion organisms—manufacturer "F"). Twelve hours later developed fever and irritability, and 24 hours later had two severe generalized convulsions. Because of the convulsions was admitted to Children's Hospital. Course: On admission he was having a left-sided convulsion. Body temperature was 39.4°C., and a left hemiparesis was found. Urine, blood Hinton, and tuberculin skin test 1-1000 were negative. WBC was 17,300 and spinal fluid was clear with total protein of 34 mg./100 cc. fluid. X-rays of the skull and long bones were negative. The fever subsided by the third hospital day, the hemiparesis improved, and the convulsive state appeared to subside. Readmitted at three years because of intermittent generalized convulsive seizures and persistent weakness of left arm, leg and left side of face. PEG (Fig. 10-a.) at this time revealed dilatation of right lateral ventricle and rather prominent subarachnoid pathways on the right. EEG showed 3-4 per second waves in precentral and occipital leads. Was discharged home without medication. Seen again at 8 5/12 years of age because of vague abdominal pain. He was attending the first grade with difficulty. A psychologic examination at this time showed a mental age of 7 4/12 years with considerable scatter and an I.Q. of 85-90. Attention spans were short, planning ability poor, and learning ability irregular. Had difficulty in organizing and analyzing form material. EEG (Fig. 10-b.) at this time showed 8-10 per second waves in occipital leads, some 6-8 per second waves, with almost continuous 18-25 per second activity in frontal leads. No seizure discharges. This was interpreted as showing mild slowing with abnormally fast activity. It was thought that the abdominal pain was of psychogenic origin, and the patient was discharged home unimproved. At 8 8/12 years in EEG showed frequent single spikes in left temporal lead and treatment with diphenylhydantoin sodium (dilantin) appeared to control the attacks of abdominal pain, and his conduct had been less impulsive since then.

#13, R.S. Male—11 months. Seen for recurrent convulsions. Family History: F., M., and one sibling living and well. Past History: Essentially normal, but mother thought he was slightly "slow" as compared to the sibling. Present Illness: At five and one-half months, in December 1944, in Salem, Mass., was given first dose of pertussis vaccine 1 cc. (concentration undetermined—manufactured either "E" or "F"). At six months received a second dose of 2 cc. of the same preparation. Twenty-four hours later had two severe generalized convulsions. Following this he seemed well but had three more generalized convulsions in the next five months. At 11 months of age development appeared normal. EEG and PEG were not done. A report from the mother states that at 2 9/12 years he was developing well and had no further seizures, since treatment with phenobarbital had been instituted.

#14, R.D. Male—17 months. Entered because of recurrent convulsions. Family History: F and M. living and well. No siblings. Past History: Normal, sat at six months. Present Illness: At six months, in May 1943, in Quincy, Mass., received first immunizing dose of 1 cc. diphtheria toxoid (alum-precipitated) and pertussis vaccine (10 billion organisms—manufacturer "G"). Twelve hours later developed fever, had a severe generalized convulsion, and swelling of the inoculated leg. The complaints subsided promptly and he appeared well. At seven months a second dose of less than 1 cc. diphtheria toxoid and pertussis vaccine (less than 10 billion organisms—manufacturer "G") was given. Again, 12 hours after this second inoculation he had generalized convulsions. Since that time had had recurrent generalized convulsions of both petit and grand mal type. Course: At 17 months, because of recurrent convulsions, was admitted to Children's Hospital. Physical examination was negative and the laboratory findings showed a negative urine and blood Hinton. WBC 12,500 with 59% polynuclear leucocytes. The spinal fluid was clear with total protein of 9.5 mg./100 cc. fluid. Psychologic evaluation revealed numerous irregularities, with short attention spans and with little learning from experience or imitation. Potential behavior level was seldom reached. EEG showed high voltage 3-5 per second waves in all leads, but no focus, and this was considered definitely slowed for age. PEG showed moderate dilatation of entire ventricular system, basal cisterns, and subarachnoid pathways.

#15, E.B. Female—11 months. Entered because of recurrent convulsions. Family History: F. M., and two siblings living and well. No history of epilepsy or convulsions. Past History: Normal. At four months she rolled over, at seven months sat alone, and at eleven months was pulling herself to her feet in her crib. Present Illness: At six months was given her first dose of 1 cc. "triple vaccine," diphtheria and tetanus alum-precipitated toxoids and alum-precipitated pertussis vaccine (10 billion organisms—manufacturer "H") without reaction. At seven months received a second dose of similar material (manufacturer "A") with some febrile response. At eight months, on April 14, 1947, in Putnam, Conn., received her third dose of 1 cc. of the original material (manufacturer "H"), and was vaccinated against small pox at the same time. About 18 hours later was found in convulsions, which were left sided at times and generalized at times, and continued for six hours intermittently, in spite of 45 mg. sodium phenobarbital intravenously. After the convulsion was stuporous for 12 hours and then showed a flaccid left hemiplegia, which cleared completely in a week. At the time of the convulsion was admitted to another hospital where, because examination disclosed redness of her throat and ears, penicillin and sulfadiazine were administered. A lumbar puncture done on the third day after the injection showed clear spinal fluid with a negative Pandy test and 63 monocytes per cmm. Cultures and guinea pig inoculations produced no growth. Blood examination the day after the inoculation showed a WBC of 9,200 of which 63% were polynuclear leucocytes, 35% lymphocytes, and 2% monocytes. Urine examination was negative. The smallpox vaccination ran the usual course of a primary reaction, and she was improving rapidly at the time of the take. Three months later developed staring spells, occurring every hour or two, for periods of several days, followed by periods of weeks when no attacks were seen. On two occasions the periods of staring spells were followed by a little diarrhea, and the last of these periods of staring spells was followed by a few days of fever, up to 37.8° C. or 38.3° C. She seemed well for a month, when staring spells developed in connection with an upper respiratory infection and fever. She had these for three days and then developed a convulsion, which began on the left, soon became generalized, and lasted several hours in spite of medication with intravenous sodium phenobarbital. Was brought to the hospital in the convulsion. Course: Physical examination showed a comatose, convulsing child with no evidence of infection. WBC was 30,100 with 85% polynuclear neutrophiles. Spinal fluid examination showed 1 mononuclear cell per cmm. and a total protein of 13.5 mg./100 cc. fluid. Cultures were sterile. The convulsion subsided soon after admission to the hospital, and after a period of stupor she again showed temporary left hemiplegia, no trace of which remained five days later. EEG showed 2½-4 per second waves, with no focus and no seizure discharges. This was considered slightly slowed for age. PEG showed slight inequality of lateral ventricles with slight blunting of right lateral ventricle. There was a good deal of subdural air, considerably greater on the left. PEG was considered normal.

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SPANISH ABSTRACT

Encefalopatias Observadas Despues del Uso Profilactico de la Vacuna Antitosferina

Durante los años de 1939 a 1947 inclusive fueron admitidos en el Hospital de Niños de Boston diez y seis casos que desarrollaron sindrome encefalitico subitamente iniciado dentro de los veiente minutos a setenta y dos horas despues de la inyeccion de vacuna pertussis preventiva.

La edad de los niños inoculados varia entre cuatro y medio y diez y ocho meses. En los niños mayores el desarrollo habia evolucionado lo bastante para presumir adecuada normalidad. Uno habia mostrado "espasmos nutans" antes de la vacunacion, pero habia caminado y pronunciado algunas palabras antes de la inyeccion. Ninguno habia tenido convulsiones antes de la inoculacion. Tres de ellos muestran en su historia familiar parientes, tias o tios, con hidrocefalia, fiebre, convulsiones, defectos mentales o epilepsia.

Seis niños reaccionaron explosivamente a la primera dosis, tres a la segunda dosis y seis a la tercera dosis. Tres niños que habian tenido convulsiones en las primeras dosis reaccionaron otra vez con convulsiones en la dosis sucesiva. Las convulsiones fueron en todos los casos el sintoma mas sobresaliente. Despues de la enfermedad aguda un niño tuvo tres convulsiones espaciadas en cinco meses pero durante los dos años siguientes se mantuvo normal. Los catorce niños restantes sufrieron de variados trastornos cerebrales cronicos: dos presentaron signos de demencia marcada en distintos periodos, terminando con la muerte, nueve mostraron una variedad de defectos, deficiencia mental,

epilepsia, paralisis cerebral y tres de ellos han sido observados demasiado recientemente para establecer una conclusion definitiva.

Durante un periodo de diez años, ocho niños con encefalomielitis consecutiva a la vacunacion fueron admitidos en el Hospital de Niños de Boston. Desde que se realiza la vacunacion virtualmente en el 100% de la poblacion, la encefalopatia consecutiva al metodo profilactico de inmunizacion contra la tosferina se observa mas frecuentemente y con mas severidad que en los casos que siguen a la vacunacion antivariolica.

Un importante riesgo de encefalopatia se observa en el uso de la vacunacion profilactica contra la tosferina. En vista de esta posibilidad y de la falta de seguridad absoluta en la eficacia de la vacuna parece que los niños estan sin embargo mas seguros vacunados que no. El presente estudio no llega a dilucidar los medios por los cuales la vacuna daña al tejido nervioso. Grandes esfuerzos para disminuir este azar, ya por modificaciones de la vacuna, o por nuevos metodos en su administracion parecen indicarlo.

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